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Review Article



# Coal Workers' Pneumoconiosis in the 21st Century: Emerging Trends, Treatment Gaps, and Prognostic Uncertainties in a Resurgent Occupational Lung Disease

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## Abstract

Coal Workers' Pneumoconiosis (CWP), once thought to be a vanishing disease in advanced economies, is experiencing a disturbing resurgence, particularly in the United States, Australia, and China. This paradox persists despite decades of regulatory efforts aimed at dust control and occupational health surveillance. Emerging data points to evolving workplace exposures, especially high-silica content in modern mining environments, and highlight a new generation of workers developing severe, rapidly progressive disease. This review synthesizes current evidence on the clinical progression, management, and long-term outcomes of CWP, with particular attention to the resurgence of Progressive Massive Fibrosis (PMF). We identify key gaps in early detection, prognostication, and therapeutic development, and outline priorities for translational and clinical research. CWP has re-emerged in high-incidence clusters with increasingly aggressive phenotypes and younger age of onset. Despite clinical severity and rising burden, there are currently no FDA-approved disease-modifying therapies for CWP. Existing surveillance tools, primarily chest radiography, are limited in sensitivity for early diseases. Prognostic modeling remains underdeveloped, with few validated biomarkers or imaging-based risk stratification tools. Research infrastructure is fragmented, and clinical trial activity remains minimal compared to other fibrosing lung diseases such as Idiopathic Pulmonary Fibrosis (IPF). There is an urgent need for integrated research efforts to develop novel therapeutics, improve early detection through advanced imaging and biomarker platforms, and implement precision medicine strategies. Addressing these unmet needs requires coordinated investment in multicenter cohorts, mechanistic studies of individual susceptibility, and translational infrastructure tailored to occupational lung disease.

**Keywords:** Pneumoconiosis, Coal Miners, Black Lung, Artificial Intelligence, Machine Learning, Prediction

## Introduction

Coal Workers' Pneumoconiosis (CWP), commonly known as "black lung disease," is a chronic, fibrotic interstitial lung disease caused by prolonged inhalation of respirable coal mine dust, often compounded by silica particles [1]. First recognized in the 19th century during the rise of industrial mining, CWP was once

considered a vanishing disease in high-income nations due to regulatory efforts and improvements in occupational dust control [2]. However, in recent decades, CWP has re-emerged as a significant public health concern, particularly in the United States, China, and Australia, underscoring both persistent exposures and scientific gaps in treatment and surveillance [3]. Despite longstanding exposure limits, the United States has witnessed a disturbing resurgence of CWP, especially in younger miners and those in central Appalachia3. Between 2000 and 2020, the prevalence of CWP among long-tenured U.S. miners nearly doubled, with the most severe form, Progressive Massive Fibrosis (PMF), increasing tenfold in some regions [4,5]. Recent data from the National Institute for Occupational Safety and Health (NIOSH) indicate that nearly 1 in 5 miners with 25 or more years of experience in central Appalachia are affected by CWP, many of whom are under the age of 50 [6]. These trends have been attributed to increased mechanization, longer shifts, and high-silica dust exposures from thin-seam mining operations, all of which may overwhelm traditional dust controls [7].

Globally, the burden of CWP remains substantial. In China, which employs over 4 million coal miners, CWP continues to be the most prevalent occupational disease. A 2020 analysis estimated that more than 800,000 workers in China live with coal-related pneumoconiosis, with over 20,000 new cases diagnosed annually despite regulatory reforms [8]. In Australia, a 2015 re-identification of CWP in Queensland after decades of dormancy triggered a national review of dust exposure limits and health surveillance programs. Since then, more than 150 cases have been confirmed, highlighting systemic gaps in monitoring and enforcement [9]. The paradox of resurgence in technologically advanced economies, despite stricter regulations and improved dust suppression technologies, suggests not only policy and enforcement failures but also a misalignment between pathophysiological knowledge and clinical practice. Moreover, surveillance systems have lagged in incorporating early biomarkers of fibrotic progression or accounting for the synergistic impact of silica exposure [10]. Equally concerning is the complete absence of FDA- or globally approved disease-modifying therapies for CWP. Management remains largely supportive, focused on symptom control, smoking cessation, supplemental oxygen, and in rare cases, lung transplantation [11]. These approaches do not address the underlying fibrotic mechanisms, nor do they prevent progression to debilitating stages such as PMF.

While progress has been made in elucidating the molecular underpinnings of fibrotic lung disease (e.g. the role of transforming growth factor-beta (TGF-β) [12], interleukin-11 (IL-11) [13], and oxidative stress) therapeutic translation in CWP has lagged behind related conditions such as idiopathic pulmonary fibrosis (IPF) [14]. In IPF, antifibrotic agents such as pirfenidone and nintedanib are now standard of care [15]. The unique immunopathology and chronic exposure dynamics of CWP call for novel, multimodal treatment strategies that can target multiple pathogenic pathways simultaneously. In addition to therapeutic gaps, prognostic uncertainty remains high in CWP. Disease progression can vary significantly even among individuals with similar exposure profiles [16]. For example, a post-COVID lung disease prediction paper in this domain has fueled a need for molecular risk stratification, precision medicine approaches, and integrative surveillance that combines occupational exposure data with biological markers and imaging [17]. Meanwhile, miners with early or moderate disease often lack access to specialty care due to geographic, socioeconomic, and regulatory barriers, particularly in rural mining regions [18].

In sum, CWP represents a paradigmatic failure of prevention, early intervention, and therapeutic innovation in occupational medicine. Its resurgence in the 21st century, amidst global technological advancement, demands a reinvigorated research agenda that couples' systems biology, artificial intelligence, and regenerative medicine with policy reform and improved surveillance. Addressing these unmet needs is not only a scientific imperative but a moral one, as it speaks about the health and dignity of workers who remain in the front lines of global energy systems.

## Pathophysiology of Coal Workers' Pneumoconiosis

CWP results from chronic inhalation of respirable coal mine dust, leading to a progressive lung disease characterized by pulmonary inflammation, fibrosis, and architectural destruction. The pathogenesis of CWP reflects a complex interplay between particulate exposure, dysregulated immune responses, and failed resolution of tissue injury [19]. While the primary insult is environmental, downstream biological cascades drive disease progression and heterogeneity in clinical outcomes.

## Dust Exposure and Lung Retention

The pathogenic potential of coal mine dust is determined by multiple factors, including particle size (<5 μm), composition (particularly silica content), concentration, and cumulative exposure duration [20]. Respirable dust particles bypass upper airway defenses and deposit in terminal bronchioles and alveoli, where they evade clearance and accumulate in pulmonary macrophages. Silica-rich coal dust, particularly from thin-seam mining, has been strongly associated with a higher risk and accelerated progression of CWP [2,5]. Once deposited, these particles persist in the lung parenchyma due to their bio-persistence and cytotoxic effects, particularly on macrophages. The failure of effective clearance leads to a cycle of persistent inflammation and progressive fibrosis that defines the pathophysiology of CWP. High cumulative exposure correlates not only with disease risk but also with radiographic severity and pulmonary function decline [4].

## Inflammatory and Fibro Genic Cascades

Dust-laden alveolar macrophages serve as the primary instigators of inflammation in CWP. Upon engulfment of coal and silica particles, macrophages undergo Reactive Oxygen Species (ROS) generation, release of lysosomal enzymes, and pyro ptosis

[21]. These events amplify the inflammatory response, leading to the recruitment of neutrophils and monocytes and activation of resident fibroblasts.

Key pro-inflammatory and pro-fibrotic cytokines include:

a) Tumor necrosis factor-alpha (TNF-α) - induces neutrophil chemotaxis, increases vascular permeability, and drives granuloma formation [22].

b) Interleukin-1 beta (IL-1β) - activates the inflammasome and perpetuates chronic inflammation [23].

c) Transforming growth factor-beta (TGF-β) - a central mediator of fibroblast activation and extracellular matrix (ECM) deposition [24].

d) Interleukin-11 (IL-11) - a recently recognized effector in pulmonary fibrosis, contributing to fibroblast proliferation and ECM remodeling [13].

In response to chronic inflammation, activated fibroblasts and myofibroblasts deposit Excessive Extracellular Matrix (ECM) components (collagen I and III), leading to progressive alveolar distortion and fibrotic remodeling [25]. Oxidative stress, driven by mitochondrial dysfunction and persistent ROS generation, further promotes epithelial cell apoptosis and mesenchymal transformation, exacerbating tissue damage [26].

## Transition from Simple to Complicated CWP (Progressive Massive Fibrosis, PMF)

CWP is typically classified into simple and complicated forms. Simple CWP is characterized by small, rounded opacities (<10 mm in diameter) predominantly in the upper lobes [27]. While often asymptomatic, it can progress over time to PMF, marked by coalescence of nodules into large fibrotic masses (>1 cm), traction bronchiectasis, and severe parenchymal destruction. The transition to PMF is driven by continued dust exposure, inadequate resolution of inflammation, and amplified fibroproliferative signaling [28]. Histologically, PMF lesions exhibit dense collagen deposition, central necrosis, and dust-laden macrophage aggregates, often accompanied by obliterative vasculopathy and bronchial distortion [29]. Once PMF is established, pulmonary function decline accelerates, with steep reductions in $FEV_1$, FVC, and DLCO. PMF is associated with high morbidity and a significant increase in all-cause mortality [5].

## Comorbidities

CWP frequently overlaps with other pulmonary and systemic pathologies, compounding diagnostic and therapeutic challenges. CWP and COPD often coexist, particularly among smokers. Smoking independently, coal dust exposure has been shown to cause small airways disease, emphysema, and chronic bronchitis-like features. Studies suggest that miners with mixed-dust pneumoconiosis frequently meet spirometric criteria for COPD, with increased airway hyperreactivity and gas exchange abnormalities [30]. High-silica content in coal mine dust increases the risk of developing accelerated silicosis, a rapidly progressive fibrosing lung disease. Silicotic nodules, hilar lymph node calcifications, and a higher frequency of PMF are hallmarks of silica-related CWP, underscoring the need for exposure profiling and stratified risk models [31]. Emerging evidence suggests that chronic particulate exposure may trigger autoimmune activation, particularly in genetically susceptible individuals. Studies have reported the increased Prevalence of Antinuclear Antibodies (ANA), rheumatoid factor, and systemic autoimmune disease (e.g., rheumatoid arthritis, systemic sclerosis) among miners with pneumoconiosis [32]. The mechanistic link may involve particulate-induced NETosis, a unique form of programmed cell death occurring in neutrophils, characterized by the release of web-like structures known as Neutrophil Extracellular Traps (NETs) [33]. Epitope spreading and chronic immune dysregulation are also implicated epitope factors.

## Current Landscape of Clinical Management

Despite the increasing clinical burden and scientific understanding of CWP, the current management paradigm remains largely supportive and palliative, with no available disease-modifying therapies. The standard of care continues to rely on radiographic surveillance, symptom control, and risk mitigation rather than pathophysiological intervention or disease reversal. As disease incidence rises, particularly in younger and more severely affected miners, there is growing urgency to transform clinical care through earlier diagnosis, more robust biomarker development, and a shift toward precision-targeted therapeutics.

## Diagnosis

The diagnosis of CWP is grounded in a combination of occupational exposure history, clinical symptoms, pulmonary function testing, and imaging, often supplemented by exclusion of other interstitial lung diseases [9,15,17]. Chest radiography, interpreted using the International Labour Organization (ILO) classification system, remains the foundational tool in epidemiologic surveillance and clinical diagnosis [34]. This semi-quantitative system classifies small opacities by shape (rounded or irregular), size, and profusion, and identifies large opacities consistent with PMF [35]. However, chest x-ray alone may underestimate early or atypical disease, particularly in individuals with high-silica exposure or those with coexisting emphysema [36]. High-Resolution Computed Tomography (HRCT) offers superior sensitivity and specificity, particularly for detecting early interstitial changes, centrilobular emphysema, and subtle PMF lesions [37]. CT-based quantitative image analysis is also emerging as a powerful tool for disease staging, longitudinal tracking, and potential integration into predictive algorithms [38].

**Emerging Biomarkers:** There is increasing interest in the use of serum and pulmonary biomarkers to aid in the early detection and prognostication of CWP. Among the most promising are:

a) Krebs von den Lungen-6 (KL-6): a mucin-like glycoprotein elevated in interstitial lung disease and correlated with fibrotic burden [39].

b) Club cell protein (CC16): a marker of epithelial injury, decreased chronic lung damage and dust exposure [40].

c) Surfactant protein-D (SP-D): associated with alveolar inflammation and fibrotic progression [41].

While these markers show potential in small observational studies, none have been validated for routine clinical use in CWP, and standardization of assays, thresholds, and clinical integration remains a challenge.

## Treatment Modalities

The current treatment framework for CWP focuses on symptom palliation, preservation of lung function, and prevention of complications, without altering the underlying fibro genic process.

**Symptom Management:** Bronchodilators, including inhaled $\beta_2$-agonists and anticholinergics, are often prescribed to address coexisting airflow obstruction or chronic bronchitis symptoms. While not disease-modifying, they may improve quality of life and exercise tolerance. Systemic corticosteroids are occasionally used in cases with acute inflammatory flares or autoimmune overlaps, although their long-term benefit in pure CWP is unproven and controversial [42].

**Pulmonary Rehabilitation:** Structured pulmonary rehabilitation programs incorporating aerobic training, strength conditioning, education, and breathing exercises have demonstrated benefit in improving functional capacity and health-related quality of life in patients with interstitial lung diseases, including CWP. However, access to rehabilitation services remains limited in many coal mining regions.

**Lung Transplantation:** In end-stage CWP with severe respiratory failure, lung transplantation may be considered. However, candidates are typically younger, non-smokers with isolated pulmonary disease and adequate social support, criteria not often met by affected miners. Data on post-transplant outcomes in CWP is sparse, and the role of transplantation remains limited and controversial [43].

## Gaps in Therapeutic Development

Despite mechanistic parallels to IPF, including activation of TGF-β signaling, fibroblast proliferation, and ECM deposition, there are no approved antifibrotic therapies for CWP. Agents such as nintedanib and pirfenidone, now standard in IPF [15], have not been formally evaluated in CWP through randomized controlled trials, in part due to regulatory and funding barriers. Furthermore, no pharmacological agent currently approved in any jurisdiction has demonstrated efficacy in halting or reversing disease progression in CWP. The therapeutic pipeline remains nearly empty, with few early-phase trials and limited investment from pharmaceutical stakeholders. This lack of progress is partly due to the orphan nature of the disease, its association with occupational exposures rather than idiopathic etiology, and historically poor engagement between academic researchers, occupational health systems, and industry partners. As a result, clinical care continues to rely on reactive strategies rather than proactive, mechanism-based interventions. This treatment gap underscores the urgent need for translational efforts to repurpose antifibrotic therapies, validate new targets (e.g., IL-11, mitochondrial ROS), and explore multimodal regimens, currently under development using AI-guided systems biology.

## Prognosis and Natural History

CWP presents a highly variable clinical course, ranging from indolent, radiographically stable simple pneumoconiosis to rapidly progressive forms culminating in PMF, respiratory failure, and premature death. The natural history of CWP is shaped by exposure intensity and duration, particle composition, coexisting pulmonary disease, and host susceptibility factors, including genetic and immunologic background. Recent trends indicate a resurgence of rapidly progressive and fatal forms of CWP, especially among younger miners exposed to high-silica dust mixtures in modern mining operations [5,8,9,16].

## Natural Progression and Clinical Phenotypes

CWP progression follows a continuum from simple pneumoconiosis, characterized by small-rounded opacities without significant impairment, to PMF, defined radiographically as large (>1 cm) fibrotic masses, typically in the upper lung zones, often associated with severe physiological and radiographic changes. While many individuals with simple CWP may remain clinically stable for decades, a significant subset, particularly those with high cumulative dust exposure or silicosis overlap, progress to PMF within 5-10 years. Pathological progression is driven by persistent alveolar macrophage activation, fibro genic cytokine signaling (e.g., TNF-α, TGF-β), and silica-induced cytotoxicity, leading to uncontrolled collagen deposition and parenchymal destruction [5,15,44]. Longitudinal spirometry and gas exchange data indicate that individuals with PMF experience accelerated annual declines in $FEV_1$ (-75-100 mL/year) and disproportionate reductions in DLCO, reflecting both airflow obstruction and destruction of alveolar-capillary interface. Mixed ventilatory defects are common in late-stage diseases, with variable responsiveness to bronchodilators. Distinct phenotypic variants of CWP are increasingly recognized. These phenotypes may inform risk stratification and therapeutic targeting as personalized models evolve.

## Mortality Trends

Mortality in CWP has demonstrated a disturbing resurgence in the past two decades, especially among Appalachian miners, reversing prior downward trends linked to regulation. Analysis

of national mortality data from 1999–2020 shows a 47% increase in age-adjusted mortality due to pneumoconiosis among miners aged <55 years [5,15,44]. Respiratory failure is the leading cause of death in severe CWP, accounting for 55–65% of pneumoconiosis-related deaths in advanced cases. Lung cancer risk is elevated in coal miners, particularly those with prolonged exposure to silica or diesel exhaust particulates, although disentangling independent effects from smoking remains difficult [45]. Cardiovascular disease represents an underrecognized contributor to mortality. Chronic hypoxemia, systemic inflammation, and occupational stressors may drive increased cardiovascular events in this population, though definitive data remain limited.

## Prognostic Markers and Risk Models

Current prognostic tools for CWP are limited in accuracy and clinical utility, often relying on crude measures such as baseline chest radiograph classification, spirometry, and exposure history. Most existing models fail to incorporate dynamic physiological changes, environmental co-exposures, or genetic susceptibility. Prediction of PMF development or rapid progression remains highly imprecise, often relying on retrospective or cross-sectional datasets. Recent advances in imaging, -omics technologies, and computational modeling offer promising avenues to personalize risk prediction and monitor disease trajectory. Quantitative Imaging such as AI-assisted CT quantification of fibrosis, emphysema, and PMF volume offers objective, reproducible metrics that correlate with lung function decline and mortality risk [46]. Preliminary studies suggest roles for genetic polymorphisms in TNF-α, TGF-β1, and inflammasome-related genes in modulating susceptibility and progression, though prospective validation is lacking [47]. Machine Learning (ML) algorithms trained on multi-modal datasets (imaging, PFTs, biomarkers) are being developed to predict PMF conversion, mortality risk, and exacerbation likelihood, though clinical implementation remains in early phases [48]. However, there remains a pressing need for robust, prospective cohorts with deep phenotyping to validate these tools and move toward precision prognostication in CWP.

## Unmet Needs and Barriers to Progress

Despite the resurgence of severe and rapidly progressive CWP, particularly among younger miners exposed to high-silica environments, research and therapeutic development continue to lag far behind that of other fibrosing lung diseases. Morbidity and mortality trends highlight the urgency of addressing longstanding translational and structural barriers that have impeded progress in prevention, early detection, and treatment. There are currently no FDA-approved disease-modifying therapies for CWP. In contrast, IPF has seen accelerated drug development with multiple successful Phase III trials and the approval of antifibrotic agents such as pirfenidone and nintedanib. These agents, which target TGF-β signaling and receptor tyrosine kinases, offer a mechanistic framework potentially relevant to CWP but remain untested in this population due to systematic exclusion from IPF trials and a lack of CWP-specific studies [3,15,21,29,35].

Preclinical translation is hampered by the absence of validated animal models that replicate key features of CWP-namely, silica-driven fibrogenesis, persistent inflammation, and gene-environment interactions associated with coal dust exposure. On the clinical side, trial readiness is hindered by the lack of validated biomarkers of progression, absence of surrogate endpoints, and variability in radiologic and physiological phenotypes that complicate enrollment and stratification. Regulatory uncertainty and limited commercial interest have further discouraged pharmaceutical investment, despite the escalating public health burden.

Current surveillance tools, including chest radiography and symptom-based screening, lack the sensitivity to detect early or subclinical disease and are susceptible to underreporting. While cumulative exposure to respirable coal mine dust is the primary risk factor, only a subset of exposed individuals develops CWP, and fewer still progress to PMF. This variability suggests an underexplored role for host susceptibility. Although the Coal Workers' Health Surveillance Program (CWHSP) has expanded to include spirometry and more frequent evaluations, substantial diagnostic delay remains. Low-Dose CT (LDCT) is significantly more sensitive for detecting early parenchymal changes, including ground-glass opacities and small PMF lesions not visible on X-ray [49]. However, LDCT is not routinely used in occupational screening due to cost, radiation exposure concerns, and lack of reimbursement frameworks. Artificial Intelligence (AI)-assisted CT interpretation, already transforming lung cancer screening, has potential for scalable implementation in occupational health but lacks validation and infrastructure for CWP-specific applications. Expanding evidence-based screening with quantitative imaging, biomarker integration, and digital platforms represents a major unmet need in early disease interception and longitudinal monitoring.

Emerging evidence points to genetic and epigenetic determinants of disease risk. Polymorphisms in TNF-α, IL-1β, and TGF-β1 have been associated with increased susceptibility in small studies, but findings lack replication in larger, diverse, or prospective cohorts [50]. Epigenetic modifications, including DNA methylation and non-coding RNA changes, are increasingly implicated in modulating silica-induced inflammation and fibrosis [50]. However, gene-environment interactions, particularly between pro-fibrotic genotypes and high-silica dust exposure, remain poorly characterized in clinical settings. Addressing these gaps is essential for advancing precision prevention and risk-adapted surveillance strategies. Identifying molecular signatures of early disease could enable stratified screening, inform chemoprevention trials, and ultimately reduce disease progression through earlier intervention.

## Limited Longitudinal Cohort Studies and Trial Infrastructure

One of the most critical impediments to scientific and therapeutic

progress in CWP is the absence of large, prospective natural history studies. In contrast to IPF and other interstitial lung diseases, which benefit from multicenter registries (e.g., IPF-PRO, Pulmonary Fibrosis Foundation Registry), CWP lacks a comparable clinical research network. For example, there is no dedicated U.S. national registry or consortium for CWP integrating clinical, radiologic, physiologic, environmental, and biologic data. Longitudinal cohort studies capturing progression from early disease to PMF, with serial CT, PFTs, biospecimens, and digital health data, are urgently needed to inform biomarkers, prognostic tools, and clinical trial design. Furthermore, the current trial infrastructure is fragmented, with few academic centers actively conducting interventional studies in CWP and limited coordination between occupational medicine, pulmonology, radiology, and industrial hygiene experts. As such, investing in clinical trials, particularly those embedded within federal surveillance programs like the CWHSP, would provide a foundation for rapid-cycle therapeutic development and regulatory engagement.

## Future Directions and Research Priorities

The CWP treatment void persists despite rising incidence, well-characterized fibro genic mechanisms, and decades of epidemiologic surveillance. Given the complex, multifactorial nature of CWP pathophysiology encompassing oxidative stress, chronic inflammation, aberrant wound healing, and progressive fibrosis, a single-agent approach is unlikely to yield meaningful disease modification. Accordingly, multimodal and systems biology–guided strategies are gaining momentum. One such approach is the development of GATC-CWP-01, a novel polypharmaceutical formulation engineered by GATC Health using Artificial Intelligence (AI)-driven predictive human biological modeling [51]. GATC-CWP-01 integrates four key pharmacological components:

a) Antifibrotic agents (e.g., nintedanib or pirfenidone) to inhibit fibroblast activation and extracellular matrix deposition

b) Benzopyrones to reduce interstitial edema and enhance macrophage function

c) Interleukin-11 (IL-11) antagonists to suppress pro-fibrotic cytokine signaling

d) Peptide-based uptake enhancers to facilitate targeted pulmonary tissue penetration.

To enhance reparative potential, this protocol is further augmented by autologous mesenchymal stem cell (MSC) therapy, administered via a single intravenous infusion following tolerability assessment of GATC-CWP-01. MSCs, derived from adipose or bone marrow sources, have shown robust anti-inflammatory, antifibrotic, and immunomodulatory effects in preclinical models of pulmonary fibrosis. The combined therapeutic strategy represents a rational, synergistic effort to modulate multiple pathophysiological pathways concurrently, restore immunological balance, and promote tissue regeneration within the pulmonary microenvironment. This paradigm exemplifies the type of next-generation translational research urgently needed in the field moving beyond single-pathway interventions toward precision-guided, multimodal disease modification. Other emerging frontiers include inhaled biologics, targeted nano therapies, and engineered extracellular vesicles.

CWP exhibits significant interindividual variability in clinical progression and response to treatment, suggesting a need for biomarker-guided stratification and molecular endotyping. Systems biology approaches such as those used in the design of GATC-CWP-01 could enable more refined patient selection, therapeutic monitoring, and adaptive dosing. We recommend a call to action for the identification of molecular signatures distinguishing indolent from rapidly progressive disease, integration of genomic, proteomic, and epigenetic data with clinical phenotypes, and use of AI-based modeling to predict treatment response and long-term outcomes. The resurgence of CWP underscores critical gaps in early detection and occupational exposure monitoring.

The time is opportune for innovation including (but not limited to) wearable real-time dust exposure sensors, enabling dynamic risk profiling, integration of occupational exposure data into Electronic Health Records (EHRs) for longitudinal tracking, and use of low-dose high-resolution CT and machine learning-enhanced imaging for earlier detection of fibrotic changes. Indeed, effective management of CWP requires a team-based approach that spans clinical, occupational, and social domains. We posit that to address the unmet needs of CWP, integration of pulmonology, occupational medicine, primary care, and palliative services, as well as assessing social determinants of health, especially in rural or underserved mining communities are essential. It is plausible that novel therapies like GATC-CWP-01 and MSC infusions and other cutting edge scientific advances paired with structural reforms have potential to achieve meaningful health impact on the underserved CWP population.

In summary, CWP remains a resurgent and under-addressed occupational health crisis. Despite a well-defined pathophysiological basis and alarming epidemiologic trends, no disease-modifying therapies are currently approved. Novel multimodal strategies such as GATC-CWP-01, in combination with autologous MSC therapy, represent a promising blueprint for therapeutic innovation, designed to modulate the complex biological networks driving disease progression. Accelerating such translational research, alongside advances in precision medicine, surveillance, interdisciplinary care, and policy reform, is essential to shift the prognosis of CWP in the 21st century.

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## Ethics Declaration

All authors declare that there are no ethical declarations to declare in relation to this manuscript.

## Competing Interests

None

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## References

1. Liu T, Liu S (2020) The impacts of coal dust on miners' health: A review. Environ Res 190: 109849.
2. Perret JL, Plush B, Lachapelle P (2017) Coal mine dust lung disease in the modern era. Respirol Carlton Vic 22(4): 662-670.
3. Han S, Chen H, Harvey MA, Stemn E, Cliff D, et al., (2018) Focusing on Coal Workers' Lung Diseases: A Comparative Analysis of China, Australia, and the United States. Int J Environ Res Public Health 15(11): 2565.
4. Almberg KS, Halldin CN, Friedman LS (2023) Increased odds of mortality from non-malignant respiratory disease and lung cancer are highest among US coal miners born after 1939. Occup Environ Med 80(3): 121-128.
5. Blackley DJ, Halldin CN, Laney AS (2018) Continued Increase in Prevalence of Coal Workers' Pneumoconiosis in the United States, 1970-2017. Am J Public Health 108(9): 1220-1222.
6. (2024) Prevalence of Pneumoconiosis and its Relationship to Dust Exposure in a Cohort of U.S. Bituminous Coal Miners and ex-Miners. National Institute for Occupational Safety and Health (NIOSH).
7. Kamanzi C, Becker M, Jacobs M, Konečný P, Von Holdt J, et al., (2023) The impact of coal mine dust characteristics on pathways to respiratory harm: investigating the pneumoconiotic potency of coals. Environ Geochem Health. 45(10): 7363-7388.
8. Wang H, Ye Q, Chen Y, Li T (2023) Epidemiology of coal miners pneumoconiosis and its social determinants: An ecological study from 1949 to 2021 in China. Chin Med J Pulm Crit Care Med 1(1): 46-55.
9. Austin EK, James C, Tessier J (2021) Early Detection Methods for Silicosis in Australia and Internationally: A Review of the Literature. Int J Environ Res Public Health. 18(15): 8123.
10. Căluțu IM, Smărăndescu RA, Raşcu A (2022) Biomonitoring Exposure and Early Diagnosis in Silicosis: A Comprehensive Review of the Current Literature. Biomedicines 11(1): 100.
11. (2025) Treating and Managing Coal Worker's Pneumoconiosis. American Lung Association.
12. Saito A, Horie M, Micke P, Nagase T (2018) The Role of TGF-β Signaling in Lung Cancer Associated with Idiopathic Pulmonary Fibrosis. Int J Mol Sci 19(11): 3611.
13. Ng B, Cook SA, Schafer S (2020) Interleukin-11 signaling underlies fibrosis, parenchymal dysfunction, and chronic inflammation of the airway. Exp Mol Med 52(12): 1871-1878.
14. Zhang Y, Wang J (2023) Cellular and Molecular Mechanisms in Idiopathic Pulmonary Fibrosis. Adv Respir Med.91(1): 26-48.
15. Bonella F, Spagnolo P, Ryerson C (2023) Current and Future Treatment Landscape for Idiopathic Pulmonary Fibrosis. Drugs 83(17): 1581-1593.
16. Chau NK, Park EK, Choi S (2025) Longitudinal analysis of coal workers pneumoconiosis using enhanced resolution-computed tomography images: unveiling patterns in lung structure, function, and clinical correlations. Front Physiol 16: 1578058.
17. Zhao Q, Li Y, Zhao C (2025) Integrating CT radiomics and clinical features using machine learning to predict post-COVID pulmonary fibrosis. Respir Res 26(1): 227.
18. Cyr ME, Etchin AG, Guthrie BJ, Benneyan JC (2019) Access to specialty healthcare in urban versus rural US populations: a systematic literature review. BMC Health Serv Res 19(1): 974.
19. Ma J, Chiu YF, Kao CC (2024) Fine particulate matter manipulates immune response to exacerbate microbial pathogenesis in the respiratory tract. Eur Respir Rev Off J Eur Respir Soc 33(173): 230259.
20. Vanka KS, Shukla S, Gomez HM (2022) Understanding the pathogenesis of occupational coal and silica dust-associated lung disease. Eur Respir Rev Off J Eur Respir Soc 31(165): 210250.
21. Adamcakova J, Mokra D (2021) New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis. Int J Mol Sci 22(8): 4162.
22. Metzemaekers M, Gouwy M, Proost P (2020) Neutrophil chemoattractant receptors in health and disease: double-edged swords. Cell Mol Immunol 17(5): 433-450.
23. Lopez-Castejon G, Brough D (2011) Understanding the mechanism of IL-1β secretion. Cytokine Growth Factor Rev 22(4): 189-195.
24. Frangogiannis N (2020) Transforming growth factor-β in tissue fibrosis. J Exp Med 217(3): e20190103.
25. Moretti L, Stalfort J, Barker TH, Abebayehu D (2022) The interplay of fibroblasts, the extracellular matrix, and inflammation in scar formation. J Biol Chem 298(2): 101530.
26. Liu S, Liu J, Wang Y, Deng F, Deng Z, et al., (2025) Oxidative Stress, Signaling Pathways, Biological Functions and Disease. MedComm 6(7): e70268.
27. Vanka KS, Shukla S, Gomez HM (2022) Understanding the pathogenesis of occupational coal and silica dust-associated lung disease. Eur Respir Rev Off J Eur Respir Soc 31(165): 210250.
28. Panagiotidis GD, Vasquez-Pacheco E, Chu X (2025) Revisiting pulmonary fibrosis: inflammatory dynamics of the lipofibroblast-to-inflammatory lipofibroblast-to-activated myofibroblast reversible switch. Front Immunol 16: 1609509.
29. Hua JT, Cool CD, Green FHY (2023) Pathology and Mineralogy of the Pneumoconioses. Semin Respir Crit Care Med 44(3): 327-339.
30. Jarrah A, Awad MT, Cramer-Bour C, Soubani AO (2024) COPD overlap conditions: Clinical and therapeutic implications. Am J Med Sci 368(6): 674-678.
31. Russell AJ, Mundt KA, Maier A (2025) Risk characterization for silica-related silicosis and lung cancer in communities adjacent to sand and gravel extraction facilities: examining limitations in our current risk methods. Front Public Health 13: 1558778.
32. Fireman EM, Fireman Klein E (2024) Association between silicosis and autoimmune disease. Curr Opin Allergy Clin Immunol 24(2): 45-50.
33. Huang J, Hong W, Wan M, Zheng L (2022) Molecular mechanisms and therapeutic target of NETosis in diseases. MedComm 3(3): e162.
34. Halldin CN, Petsonk EL, Laney AS (2014) Validation of the international labour office digitized standard images for recognition and classification of radiographs of pneumoconiosis. Acad Radiol 21(3): 305-311.

35. Weissman DN (2022) Progressive massive fibrosis: An overview of the recent literature. Pharmacol Ther 240: 108232.

36. Gredic M, Karnati S, Ruppert C, Guenther A, Avdeev SN, et al., (2023) Combined Pulmonary Fibrosis and Emphysema: When Scylla and Charybdis Ally. Cells 12(9): 1278.

37. Hatabu H, Hunninghake GM, Richeldi L (2020) Interstitial lung abnormalities detected incidentally on CT: a Position Paper from the Fleischner Society. Lancet Respir Med 8(7): 726-737.

38. Paudyal R, Shah AD, Akin O (2023) Artificial Intelligence in CT and MR Imaging for Oncological Applications. Cancers 15(9): 2573.

39. Millan-Billi P, Castellví I, Martinez-Martinez L (2024) Diagnostic Value of Krebs von den Lungen (KL-6) for Interstitial Lung Disease: A European Prospective Cohort. Arch Bronconeumol 60(6): 350-355.

40. Neumann S, Casjens S, Hoffmeyer F (2024) Club cell protein (CC16) in serum as an effect marker for small airway epithelial damage caused by diesel exhaust and blasting fumes in potash mining. Int Arch Occup Environ Health 97(2): 121-132.

41. Sorensen GL (2018) Surfactant Protein D in Respiratory and Non-Respiratory Diseases. Front Med 5: 18.

42. Håkansson KEJ, Skov IR, Andersen SAW (2025) Prevalence, Change and Burden of Systemic Corticosteroid Use in Type 2 Inflammation Associated Diseases Over 25 Years - A Nationwide Danish Study. J Asthma Allergy.18: 967-981.

43. Nandavaram S, Mei X, Khan T (2024) Outcomes of Lung Transplantation in Coal Workers Pneumoconiosis: Analysis of UNOS Database. Clin Transplant 38(12) : e70042.

44. Chang S, Wen S, Zhang W (2025) The updated evidence of pirfenidone treated silicosis based on network pharmacology, molecular docking and experimental validation. Front Med 12: 1573241.

45. Taeger D, Pesch B, Kendzia B (2015) Lung cancer among coal miners, ore miners and quarrymen: smoking-adjusted risk estimates from the synergy pooled analysis of case-control studies. Scand J Work Environ Health 41(5): 467-477.

46. Hsia CCW, Bates JHT, Driehuys B (2023) Quantitative Imaging Metrics for the Assessment of Pulmonary Pathophysiology: An Official American Thoracic Society and Fleischner Society Joint Workshop Report. Ann Am Thorac Soc 20(2): 161-195.

47. Zhang Y, Sun D, Song Y, Ye Q (2024) Candidate gene polymorphisms associated with silicosis and coal workers' pneumoconiosis: a systematic review and meta-analysis. BMC Pulm Med 24(1): 580.

48. Wu Q, Guo H, Li R (2026) Multimodal data-driven multitask learning for enhanced identification and classification of chronic obstructive pulmonary disease: a retrospective study. J Glob Health 16: 04028.

49. Yip R, Jirapatnakul A, Hu M (2021) Added benefits of early detection of other diseases on low-dose CT screening. Transl Lung Cancer Res 10(2): 1141-1153.

50. Yadav SRM, Goyal B, Mamgain G (2023) Genetic Variations in IL-1β, TNF-α, and TGF-β Associated with the Severity of Chronic Cervical Spondylitis in Patients. Cells 12(12): 1594.

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